

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Hideaki NOMURA *et al.*

Serial No.: 09/720,970

Group Art Unit: 1616

Filed: January 3, 2001

Examiner: Sharmila S. Gollamudi

For: POWDERY PREPARATION FOR MUCOSAL ADMINISTRATION CONTAINING
POLYMERIC MEDICINE

DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Hideaki Nomura, declare that

1. I am a citizen of Japan and am employed as a product planner in the Pharmaceutical Division of Kirin Beer Kabushiki Kaisha, at 26-1, Jingumae 6-chome, Shibuya-ku, Tokyo, 150-8011, Japan. I was transferred from Iyaku Kaihatsu Kenkyusho (Pharmaceutical Research Laboratory), Kirin Beer Kabushiki Kaisha, 3 Miyaharamachi, Takasaki-shi, Gunma 370-1295, Japan on November 1, 2001. I graduated from Science University of Tokyo, where I obtained a master's degree in Pharmaceutical Science in 1988 and pharmacist license in 1986. At Kirin Beer Kabushiki Kaisha, I studied the pharmaceutical formulations of new chemical and protein therapeutic agents.

2. I am a co-inventor of U.S. application serial No. 09/720,970, "*Powdery Preparation For Mucosal Administration Containing Polymeric Medicine*," filed on January 3, 2001.

3. The powder of present claim 1 is an intimate admixture of a medicine that has a molecular weight (MW) greater than 1000 and an aminoalkylmethacrylate copolymer. We unexpectedly discovered that the presence of the cationic copolymer, alongside the medicine, enhances the transmission of the medicine across the mucosal membrane. This result is very likely due to the fact that the mucosal membrane is simultaneously exposed to the medicine and methacrylate and, therefore, subjected to their respective activities concurrently.

4. By contrast, the respective activities of the coating and the drug in Norling's (U.S. Patent No. 5,958,458) formulation are temporally and functionally disconnected and distinct. One obvious reason for this disconnect is that the methacrylate copolymer is a *gastro-soluble* film coating. Accordingly, after administration, the "Eudragit® E" coating disintegrates away from the pellet, exposing the drug to the gastrointestinal system. Röhm America, Degussa, who manufactures Eudragit® E state on their website (Exhibit B) that the Eudragit® E100 product is a "protective

coating” comprising “pH dependent cationic polymer granules soluble in gastric fluid up to pH 5.0 – swellable and permeable above pH 5.0 for taste and odour masking applications.”

5. Another reason why Norling’s “coated core” pellets would not have the beneficial properties prescribed by the presently claimed powder, lies in the structure of those pellets. These comprise solid inert carrier “cores” that are layered with an active substance (column 2, lines 10-21). The resultant spherical pellet is then coated with a protective or release-modifying film using a “fluidized bed apparatus.” Without the solid core, it would be difficult, if not impossible, for the pellets to withstand the coating process (column 2, lines 33-39). See Exhibit A, a schematic comparison of the claimed admixture and Norling’s cores.

6. Norling states that the purpose of the coating is to provide “the desired release profile of the active substance included in the cores, or alternatively mask the taste of the bad-tasting active substances . . . the cores may contain two or more layers of coating” (column 8, lines 43-50). Norling classifies “acrylate polymers (such as, e.g. Eudragit® E)” as a “film coating” (column 9, lines 43-49) and “acrylic resins (Eudragit® RL and RS)” as “modified release coatings” (column 10, line 17).

7. Norling in no way teaches that the film coating material can be used for a purpose other than as a veneer over the drug-carrier core. For instance, Norling does not suggest filling the core with inert carrier, active substance, *and* Eudragit® E. Norling actually does contemplate admixing the coating material with “various excipients” but not with an active substance. Hence, Norling states that the coating may be admixed with only “plasticizers,” anti-adhesives,” “colourants,” and “solvents” (column 10, lines 35-39).

8. Norling only refers to Eudragit® E parenthetically and only then in passing. Another eight types of film coating compounds are suggested by Norling, including ethylcellulose and polyethylene glycol (column 9, lines 42-49), but there is no suggestion to use one, *i.e.*, Eudragit® E, over another, or to mix it directly with the active substance in the core. Furthermore, Examples 10 and 12 use Eudragit® RS, a “modified release coating,” which is a different combination of methacrylates than those recited in present claim 1.

9. In terms of methodology, Norling produces a suspension of theophylline (active ingredient) and calcium carbonate (inert carrier) that is spray-dried to form theophylline/inert core pellets, 158 μm in size (Example 3, column 26, lines 8-67). Norling then uses the fluidized bed apparatus to apply a 10 μm -thick film coating of Eudragit® RS solution to the theophylline core pellets (Example 10, column 32, lines 13-66). The coated theophylline cores are then formed into tablets by “direct compression” (Example 12, column 35, line 34 to column 36, line 30). Norling

concludes that, in tablet form, "the coating applied is very flexible and the release characteristics of the film are maintained even after compression" (column 36, lines 17-20).

10. By contrast, our powder composition is different because our disclosed method requires (i) mixing a solution of Eudragit® E100 directly with a buffer solution of high MW medicine, and then (ii) spray-drying the resultant liquid to produce a powder for pernasal administration. See, Examples 3 to 10 at pages 16 to 19 of the present specification.

11. Accordingly, the admixed powder composition of claim 1 is structurally and functionally distinct from Norling's "multiple unit particulate" formulation. Furthermore, there is no suggestion to include Eudragit® E100 in Norling's unit core along with the inert carrier and active substance. To have done so would have been nonsensical, since Norling teaches the film coating is used to protect the pre-formed, solid drug cores prior to tablet formation and administration.

I hereby declare that all the statements made herein of my known knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

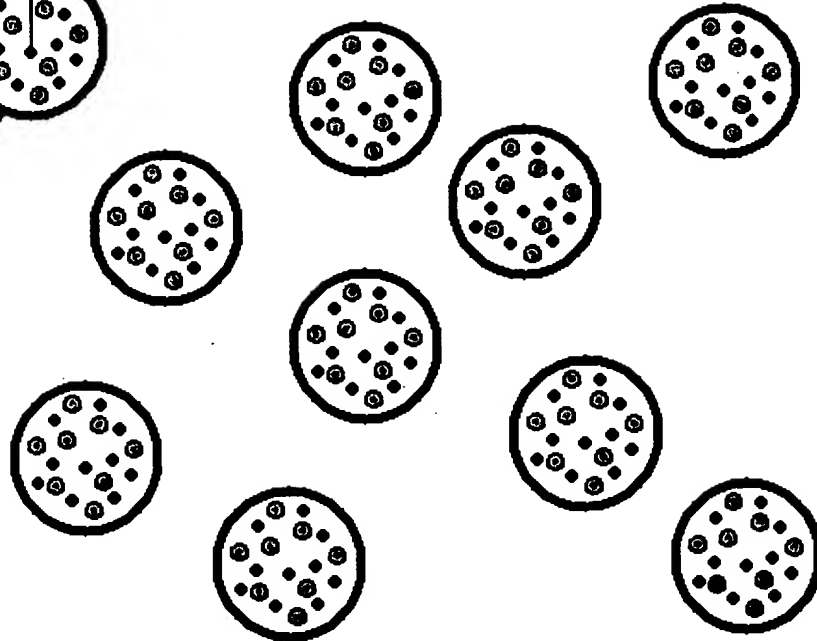
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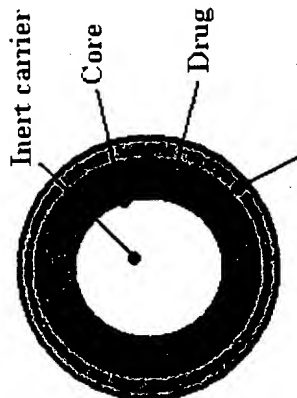
PRESENT CLAIM 1

A 'particle'
 High MW medicine molecule
 aminoalkylmethacrylate copolymer molecule



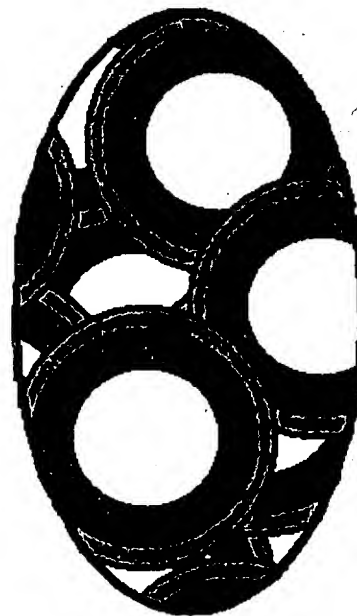
INTIMATE ADMIXTURE
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 METHACRYLATE
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 PARTICLE POWDER

NORLING



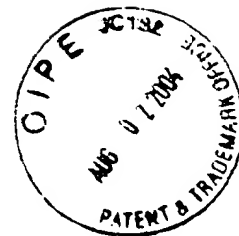
Film coating

compressed into
 tablet form



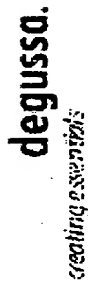
TABLET
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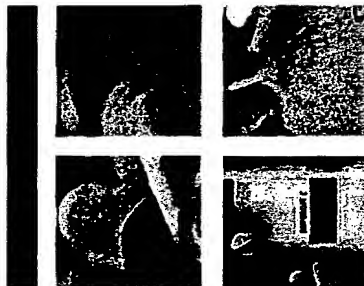
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Protective Coatings - Product Overview

pH dependent cationic polymer solution soluble in gastric fluid up to pH 5.0 – swellable and permeable above pH 5.0 for taste and odour masking applications.

EUDRAGIT® E 12,5

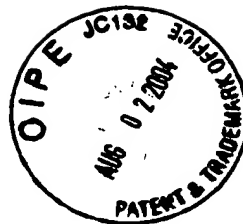
pH dependent cationic polymer granules soluble in gastric fluid up to pH 5.0 – swellable and permeable above pH 5.0 for taste and odour masking applications.

EUDRAGIT® E 100

pH dependent cationic polymer powder for aqueous formulations, soluble in gastric fluid up to pH 5.0, for moisture barrier and taste masking.

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